KINASE MUTATION-ASSOCIATED NEURODEGENERATIVE DISORDERS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of and priority to U.S. Provisional Patent Application No. 62/550,536, filed Aug. 25, 2017, the entire contents of which are incorporated herein by reference.

STATEMENT OF RIGHTS UNDER FEDERALLY-SPONSORED RESEARCH

[0002] This invention was made with government support under grant number CA008748 awarded by the National Institutes of Health. The government has certain rights in the invention.

TECHNICAL FIELD

[0003] The present disclosure relates to a method for treatment of neurodegenerative disorders.

BACKGROUND

[0004] The pathophysiology of neurodegenerative diseases is poorly understood and therapeutic options are few. Neurodegenerative diseases are hallmarked by progressive neuronal dysfunction and loss, and chronic glial activation. Whether microglial activation, which is viewed in general as a secondary process, is harmful or protective in neurodegeneration remains unclear.

[0005] BRAF is a serine/threonine-protein kinase that is part of the RAS/MAPK/ERK signaling pathway, which affects cell senescence or proliferation, differentiation, and secretion, depending on the cell type. The $BRAF^{V600E}$ point mutation results in constitutive ERK activation, and is present in numerous tumors including melanomas, thyroid, colon and liver carcinoma, and hairy cell leukemia (HCL), as well as in clonal macrophage disorders known as histiocytoses. Histiocytoses display considerable heterogeneity in terms of prognostic and clinical presentation, and are characterized by the occurrence of neurodegenerative syndromes. Microglia belong to the lineage of tissue macrophages that develop during organogenesis from yolk-sac erythro-myeloid progenitors (EMPs) distinct from haematopoietic stem cells. However, the cellular consequences of $BRAF^{V600E}$ expression in microglia and the role of BRAF inhibitors for treating neurodegenerative disease have not been investigated.

SUMMARY

[0006] The technology of the present disclosure is based on the observation that the conditional expression of a $BRAF^{V600E}$ allele in a small number of erythro-myeloid progenitors (EMPs) does not grossly affect embryonic development, but results in the accumulation of $BRAF^{V600E}$ macrophage clones in various tissues and causes neurodegeneration.

[0007] By developing novel genetically and phenotypically accurate murine models of disease, it is possible to comprehensively explore the effects of $BRAF^{V600E}$ expression in tissue macrophages and other myeloid cells. The animal model described herein overcomes a limitation of previous murine models where constitutive expression of Cre resulted in a very high frequency of cells expressing $BRAF^{V600E}$ within hematopoietic cells of different lineages, which may not accurately model the behavior of a limited number of $BRAF^{V600E}$ progenitors of a particular hematopoietic lineage in competition with wild type progenitors in patients.

[0008] In one aspect, the present disclosure provides a method for treating or preventing $BRAF^{V600E}$-associated neurodegenerative disease in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a BRAF, MEK, and/or CSF-1R inhibitor or a pharmaceutically acceptable salt thereof. In some embodiments, at least a portion of the resident macrophages in the central nervous system of the subject are $BRAF^{V600E+}$.

[0009] In one aspect, the present disclosure provides a method for treating or preventing $BRAF^{V600E}$-associated neurodegenerative disease comprising: (a) isolating resident macrophages from a neuronal environment of the subject; (b) determining whether the resident macrophages express $BRAF^{V600E+}$; and (c) administering to the subject a therapeutically effective amount of a BRAF, MEK, and/or CSF-1R inhibitor, or a pharmaceutically acceptable salt thereof, when the isolated resident macrophages express $BRAF^{V600E+}$.

[0010] In some embodiments of the methods disclosed herein, the neurodegenerative disease is characterized by one or more of impaired cognitive functions, dementia, ataxia, dysarthria, reduced motor coordination and synchrony as compared to a normal control subject, paralysis, microglia accumulation, astrogliosis, microglia phagocytosis, demyelination, neuronal loss in the central nervous system, synaptic loss in the central nervous system, and amyloid precursor protein (APP) deposits in the brain.

[0011] In some embodiments of the methods disclosed herein, the BRAF inhibitor is selected from the group consisting of vemurafenib, dabrafenib, encorafenib, PLX7904, PLX8394, GDC-0879, LGX818, and PLX4720, the MEK inhibitor is selected from the group consisting of AZD8330, refametinib, E6201, MEK162 (binimetinib), PD0325901, pimasertib, R04987655, selumetinib, TAK-733, GDC-0623, WX-544, cobimetinib, and trametinib, and the CSF-1R inhibitor is selected from the group consisting of GW2580, BLZ945, pexidartinib (PLX3397), ARRY-382, PLX7486, and JNJ-40346527. In some embodiments, the BRAF inhibitor is vemurafenib. In some embodiments, the BRAF inhibitor is PLX4720.

[0012] In some embodiments of the methods disclosed herein, the route of administration of the BRAF, MEK, or CSF-1R inhibitor is parenteral, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, oral, sublingual, intranasal, intracerebral, intrathecal, intravaginal, transdermal, rectal, by inhalation, or topical.

[0013] In some embodiments of the methods disclosed herein, treatment of the neurodegenerative disease comprises one or more of improving cognitive functions, reducing dementia, reducing ataxia, reducing dysarthria, increasing motor coordination and synchrony, relieving paralysis, reducing microglia accumulation, reducing astrogliosis, reducing microglia phagocytosis, reducing demyelination, reducing neuronal loss, reducing synaptic loss, or reducing amyloid precursor protein (APP) expression in the brain as compared to an untreated control.

[0014] In one aspect, the present disclosure provides a method for treating or preventing neurodegenerative disease